Remarks

Claims 1-9, 11-13, and 19-21 are pending. Claims 7-9, 20 and 21 were amended to be in independent form including all of the limitations of the base claim and any intervening claims.

The clean copy of the amended claims has been clarified in response to the Advisory Action.

The present invention is directed to methods for reducing blood loss from microvascular bleeding due to wounds caused by surgery or trauma. The methods and compositions are particularly useful in treating microvascular bleeding from skin graft donor sites, burns, bleeding liver surfaces, and inflamed visceral surfaces. Reduction of blood loss from microvascular bleeding depends upon effectively attenuating or ceasing anticoagulation. The invention is not the discovery of the coagulation process, or components thereof. It is the discovery that it is possible to inhibit a single component of the process and thereby inhibit microvascular bleeding. The Board of Appeals has already determined that the claimed method is both enabled and novel and non-obvious over the prior art. The only issue at this time is whether or not the applicant has complied with the written description requirement.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6, 11-13, and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed

invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

In *Enzo Biochem*, the Federal Circuit held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). The Federal Circuit held that a patentee complied with the written description requirement by depositing biological material in a public depository. The specification described the nucleotide sequence in terms of its ability to bind to *N. gonorrhoeae*. The patent had issued with no written description rejection. Nevertheless, the Federal Circuit had determined in *Enzo I* that, because the inventor had not described the actual nucleotide sequence of the probes in the patent specification, the written description was inadequate as a matter of law. In *Enzo II*, the Federal Circuit rejected its narrow interpretation of *Eli Lilly* that the disclosure of the sequence was always necessary, and instead adopted a broader interpretation of the types of disclosures that comply with the written description requirement. The court adopted provisions from the Guidelines issued by the U.S. Patent and Trademark Office that state that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. The court found that the written description requirement was met when, in the

knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure.

This standard has been reviewed and clarified further in the recent decision of Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003). This decision was the appeal of a lengthy district court ruling on validity, infringement, and enforceability of five Amgen patents relating to production of erythropoietin (EPO), a hormone that controls formation of red blood cells. Amgen's EPO is sold under the brand name EPOGEN®. Amgen asserted that Hoechst (now Aventis Pharmaceuticals, Inc.) and Transkaryotic Therapies ("TKT") infringed U.S. Patent Nos. 5,547,933; 5,618,698; 5,621,080; 5,756,349; and 5,955,422, due to the filing of TKT's Investigational New Drug Application (INDA). All of the patents shared the same disclosure. TKT recombinantly produced EPO using a method that differed from the method used by Amgen and described in the patents. TKT inserted a promoter which caused the expression of ordinarily unexpressed endogenous (or "native") EPO DNA in human cells to produce the EPO.

The Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112. In rendering its decision, the Court continued in the manner of *Enzo II* and applied a broad interpretation of the types of disclosures that comply with the written description requirement.

TKT asserted that claims did not meet the written description requirement since Amgen had failed to describe the use of all mammalian and vertebrate cells, relying on the earlier *Lilly* decision.

Relying heavily on the expert testimony provided in the District Court proceeding, the Federal Circuit held that this description adequately supports the claims covering EPO made using the genus vertebrate or mammalian cells.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001).

Analysis of the Instant Specification

The specification need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001). The applicant respectfully submits that this requirement has indeed been met in the instant application. The instant application, as the Examiner has already readily admitted, provides adequate written description of antibodies which bind to members of the anticoagulant pathway as recited in claim 1. However, Applicant is not claiming a composition.

Applicant is claiming a method. Applicant has demonstrated with an ***example*** using an antibody to protein C that the claimed method works.

In view of the foregoing legal standard, the applicant additionally, and respectfully, submits that the USPTO has clearly stated its position for applying the written description guidelines, wherein "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigens were implicitly disclosed as a result of the isolation of antigen X." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines"). The anti-coagulation factors (protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor) were well known, well characterized, and isolated targets of the claimed inhibitory compounds. The applicant submits that these factors represent "antigen X" in the USPTO's example that provides their position regarding written description. Therefore, applicant is entitled to broadly claim the inhibitors of these proteins since these would be readily available to those skilled in the art.

Applicant has demonstrated with an *example* using an antibody to protein C that the claimed method works. Applicant has described a number of other components of the coagulation pathway that can be inhibited in the claimed method other than protein C. Just as the antibody to protein C was known to those skilled in the art at the time the application was filed, so were inhibitors of these other components of the coagulation process. What was not known was the method. This is extremely important in analyzing the claims under 35 U.S.C. 112.

The Examiner has stated that the applicant has referred to a variety of different references that were published after the effective filing date of the instant application (July 24, 1992). However, the Examiner has failed to comment on any of the previously submitted references (submitted with the applicant's Response on September 23, 2002; published before the effective filing date) *as they relate to known compounds shown to inhibit specific factors of the anti-coagulation cascade via their complementarity determining regions (i.e. antigen binding sites).* These known antigen binding sites provide additional "arsenal" to one of ordinary skill in the art aiming to inhibit known and well characterized targets. Not only were the target's known and well characterized, but examples of inhibitory molecules and their recognition/binding portions were also known, thereby providing known structural interfaces between "target" and "inhibitor" (the references are: G.J. Broze (*Seminars in Hematology*, Vol. 29 (3):159-169, 1992); the abstract by Hrkal et al., (*J. Histochem. Cytochem Hybridoma*, 1991(5)633-640); the abstract by Labarrere et al., (*J. Heart Lung Transplant.* 1992(2 pt. 1):342-347); the abstract by Toulon et al.,(*J. Chromatography*, 1991(2):493-500); the abstract by Gibson et al., *(Thromb. Haemost* 1992(5):507-509); and the abstract by He et al., (*Kidney Int.*, 1992(5):1170-1174). The applicant submits that the combination of *known* antigenic anti-coagulation targets, *known* CDRs/antigenic sites of *known* inhibitors, the specification, and *known* assays (see, for example, *Thromb. Haemost*, 1993, 70(3): 448-453), clearly provides one of ordinary skill in the art with the realization that the Applicant is in possession of the method as claimed.

Claim Objections

Claims 7-9, 20 and 21 were objected to as being dependent upon a rejected base claim. The claims have now been written in independent form. As noted above, the clean copy of claim 7 has been clarified in response to the Advisory Action.

Entry of these amendments to facilitate appeal is requested.

Allowance of claims 1-9, 11-13, and 19-21 is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, April 17, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Jean Hicks

Date: April 17, 2003

Marked Up Copy of Claims as Amended Pursuant to 37 C.F.R. 1.121(c)(1)(ii)

1. (three times amended) A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. The method of claim 1 wherein the anticoagulant is protein C.

3. (amended) The method of claim 1 wherein the inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. (Amended) [The method of claim 2 wherein the inhibitor is] A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in

human plasma, wherein the compound is an antibody that inhibits protein C anticoagulant [an antibody to protein C].

8. (Three times amended) [The method of claim 7 wherein the inhibitor is] A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an antibody that inhibits protein C anticoagulant, and wherein the compound is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. (Amended) [The method of claim 8] A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding, wherein the compound is an antibody that inhibits protein C anticoagulant, and wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. (Amended) The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. (Amended) The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. (Amended) The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

19. The method of claim 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. (Amended) [The method of claim 3 wherein the inhibitor] A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is a monoclonal antibody immunoreactive with protein C and [blocking] blocks protein C activation, and wherein the compound is administered systemically.

21. (Amended) [he method of claim 20] A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is a monoclonal antibody immunoreactive with protein C and blocks protein C activation, wherein the compound is administered systemically and wherein the [inhibitor]

compound is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.